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Anne Tuazon

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Q. Liu *et al.*

Application No.: 09/989,994

Filed: November 20, 2001

For: POSITION DEPENDENT RECOGNITION OF GNN NUCLEOTIDE TRIPLETS BY ZINC FINGERS

Examiner: Karen C. Carlson

Group Art Unit: 1653

Confirmation No.: 1661

PETITION UNDER 37 C.F.R. §§ 1.144 & 1.181, CORRECTION OF IMPROPER ELECTION AND RESPONSE TO OFFICE ACTION

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This communication is in response to an Office Action dated March 18, 2004 and is accompanied by a petition and fee for a one-month extension of time, making a response due on or before July 18, 2004. Inasmuch as July 18 falls on a Sunday, the deadline for response is Monday, July 19, 2004. Accordingly, this communication is timely filed.

Remarks begin on page 2 of this paper.

REMARKS

Status of the claims

Claims 1-49 are presently pending. Claims 2-7, 9-18, 20-22 and 24-49 have been withdrawn from consideration as a result of a final restriction requirement, from which Applicants petition (see below). Accordingly, claims 1, 8, 19 and 23 were examined on the merits. Claims 1, 8, 19 and 23 were variously rejected under 35 U.S.C. §§ 101, 102, 112 and the judicially-created doctrine of obviousness-type double patenting.

Applicants note that their previous election appears to have been improper in not selecting one of the choices presented by the Office (see below) and, in this response, make a proper election consistent with the choices that were provided in the Restriction Requirement. As a result, Applicants believe that, subsequent to entry of this Response, claims 1, 5, 6 and 7 will be under consideration.

Petition from Final Restriction Requirement

Applicants timely traversed the Restriction Requirement dated December 22, 2003, in a Response filed on January 22, 2004. In an Office Action dated March 18, 2004, the Restriction Requirement was made final. Applicants hereby petition the Director to review and withdraw the Final Restriction Requirement.

A. Claimed subject matter

The claimed subject matter embraces a number of non-naturally-occurring proteins; each protein comprising three zinc fingers (denoted F1, F2 and F3 in order of progression from the amino- to the carboxy-terminus of the protein) and each protein engineered to bind a DNA target site having the nucleotide sequence GNNGNNGNN. The target site comprises three 3-nucleotide subsites, each having the sequence GNN. These subsites are denoted S1, S2 and S3; with the sequence of each subsite being read in the 5' to 3' direction (*i.e.* 5' GNN-3') but the subsites occurring in the target site in a 3' to 5' direction (*i.e.*, 5'-S3-S2-S1-3'). The claims further recite that each subsite is bound primarily by a single zinc finger and that binding of a zinc finger to a subsite depends on:

1. the nucleotide sequence of the subsite, and

2. the location of the subsite within the target sequence; *i.e.*, whether the subsite is present at position S1 (in which case it is bound by F1 of the protein), S2 (in which case it is bound by F2 of the protein) or S3 (in which case it is bound by F3 of the protein).

For example, for a target site having the sequence GAGGGTGAT (*i.e.*, S1=GAT, S2=GGT and S3=GAG), the claims specify a zinc finger protein in which F1 contains the amino acid sequence QSSNLAR (which binds the GAT subsite), F2 contains the amino acid sequence TSGHLSR (which binds the GGT subsite), and F3 contains the amino acid sequence RSDNLTR (which binds the GAG subsite). *See* claims 1, 7, 11 and 23. By contrast, for the target site GGTGATGAG, which contains the same three subsites in a different order, the claims specify a zinc finger protein in which F1 contains the amino acid sequence RSDNLAR (which binds the GAG subsite), F2 contains the amino acid sequence TSGNLVR (which binds the GAT subsite) and F3 contains the amino acid sequence TSGHLVR (which binds the GGT subsite). *See* claims 1, 5, 12 and 24. It can be seen from this example that, when the sequence GAT is present at S1, it is bound by the amino acid sequence QSSNLAR from F1, but when the same sequence is present at S2, it is bound by TSGNLVR from finger 2 of the protein; showing that binding to GNN subsites by zinc fingers can be position-dependent.

Consonant with the inventors' discovery of this position-dependence, the claims recite a 7-amino acid zinc finger sequence for binding each of the sixteen possible GNN triplets at each of the three possible locations of the triplet in the target site GNNGNNGNN, except for target sites in which S3 is GGC or GTA, or which contain GTT at any of S1, S2 or S3.

B. Restriction Requirement

In an Office Action dated December 22, 2003, the claims were subjected to a 90-way restriction. The Restriction Requirement asserted that each of the 45 claimed amino acid sequences[1] was a separate invention. Curiously, Applicants were then instructed to

[1] Applicants note that, because zinc finger sequences recognizing GTT were not claimed, nor were zinc finger sequences recognizing GGC or GTA at S3, only 43 amino acid sequences (48-5) were claimed.

select one of fifteen arbitrarily-assembled combinations of the claimed amino acid sequences for further prosecution. The claimed amino acid sequences were combined in a way that generated proteins that bind to a target site containing three copies of the same subsite (*e.g.*, proteins that bind to target sites having the sequence GAAGAAGAA, GAGGAGGAG, GACGACGAC, GATGATGAT, *etc.*).

In support of restriction among the different claimed sequences, the Office stated that "[t]he proteins of inventions 1-45 are patentably distinct because the claimed zinc fingers differ in structure and in function, ie, binding to different S target sites."

Additional restriction was required between zinc finger proteins and nucleic acids encoding these proteins. Although the Office admitted that the claimed nucleic acids are related to the claimed proteins by virtue of the nucleic acids encoding the proteins, it was argued that they are nonetheless distinct because "the protein product can be made by another and materially different process, such as by **synthetic peptide synthesis** or **purification from the natural source**. Further, the DNA may be used for processes other than the production of the protein, such as **nucleic acid hybridization assay**." (emphases added).

Moreover, and similar to its treatment of the claimed proteins, the Office asserted, on the one hand, that the claimed nucleic acid sequences encompassed 45 separate inventions and, on the other hand, organized the nucleic acid claims into 15 arbitrary groups. It was also asserted that the different nucleic acid sequences "differ in structure and function, ie, the zinc [fingers] bind to different S target sites."

C. Traversal of Restriction Requirement

The Restriction Requirement was timely traversed in a Response dated January 22, 2004. A summary of the arguments in support of traversal is given below, see Applicants' Response of January 22, 2004 for details.

1. The Office improperly prevented Applicants from clearly and distinctly claiming their invention, by refusing to examine as a whole that which they regard as their invention.

2. All claimed proteins have the same structure (a three-finger, non-naturally-occurring zinc finger protein) and the same function (DNA binding).

3. All claimed nucleic acids have the same structure (a nucleotide sequence that encodes a three-finger, non-naturally-occurring zinc finger protein) and the same function (encoding a zinc finger protein).

4. The Office's assertion, in support of restriction between the claimed proteins and the claimed nucleic acids, that the "protein product can be made by another and materially different process, such as by synthetic peptide synthesis or purification from a natural source" is unfounded. Applicants presented evidence that synthetic peptide synthesis techniques are not routinely capable of generating functional peptides having the length of the claimed proteins, and also pointed out that, since the claimed proteins are non-naturally-occurring, it would be impossible to obtain them from a natural source.

5. It was also erroneous for the Office to assert, in support of restriction between proteins and nucleic acids, that "the DNA may be used for processes other than the production of the protein, such as nucleic acid hybridization assay." Since the claimed nucleic acids encode non-naturally-occurring proteins, it is difficult to imagine what the target of such a hypothetical hybridization assay would be, nor was any hypothetical target specified by the Office.

6. The Office had used "throwaway" utilities which were not specific, substantial or credible, to support an improper Restriction Requirement.

7. The claimed proteins and the claimed nucleic acids can be used in the same method, *viz.* modulation of gene expression.

8. Applicants requested that the Office provide evidence that synthetic peptides longer that 90 amino acid residues could have been generated, in high yield and purity, by automated synthesis techniques available at the time the present application was filed.

9. Applicants requested that the Office identify a natural source of the claimed proteins and nucleic acids.

10. Applicants requested that the Office provide evidence that one of skill in the art would have recognized, as of the filing date, that a nucleic acid encoding a non-

naturally-occurring protein could have been used in a hybridization assay, and identify the target of any such hybridization assay.

D. Requirement Made Final

In an Office Action dated March 18, 2004, the Examiner stated that the arguments supporting Applicants' traversal were not persuasive, and made the Restriction Requirement final.

E. Petition for Review

1. *The Requirement is unclear*

As a threshold matter, the Restriction Requirement is unclear in asserting that there are 45 claimed amino acid sequences, when only 43 sequences are claimed. The Restriction Requirement is also unclear in stating, on the one hand, that each of the 45 claimed sequences is a different invention and, on the other, requiring election of one of fifteen different groups.[2] Inasmuch as any restriction requirement may have later ramifications on the prosecution of this and related applications (for example, with respect to double patenting issues) and in light of the decision in *Geneva Pharmaceuticals Inc. v. GlaxoSmithKline*, 349 F.3d 1373; 68 USPQ2d 1865 (CAFC 2002), clarification of the Restriction Requirement, if maintained, is requested by Applicants.

2. *Applicants have been prevented from claiming their invention*

As outlined above, the pending claims are directed, *inter alia*, to zinc finger proteins capable of binding to any target site having the sequence GNNGNNGNN, by virtue of said proteins comprising three engineered zinc fingers, each of which binds, in a position-dependent fashion, to a GNN triplet subsite. By arbitrarily restricting prosecution, in this and all continuing applications, to proteins which bind only to target sites containing three subsites of identical sequence, the Office has prevented Applicants from ever claiming proteins which bind to target sites containing non-identical subsites;

[2] for each of the sets of nucleic acid and protein claims

thus improperly prohibiting Applicants from claiming the full scope of this aspect of their invention.

MPEP 803.02 states, in part:

> . . . it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. [citations omitted] Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.

In the present case, all claimed proteins share the common utility of sequence-specific DNA-binding, and possess a substantial structural feature, namely a set of three zinc fingers, that is disclosed as being essential to that utility (*see*, for example, page 14, lines 10-15 and page 15, lines 5-31 of the specification).

The claimed amino acid sequences do not differ in structure or function, as asserted by the Office: they differ only in sequence. All claimed amino acid sequences represent the portion of the zinc finger (the "recognition helix") that is involved in sequence-specific DNA recognition and binding. Correlation between the structure of the recognition helix and its DNA recognition function is provided, for example at page 1, line 30 through page 2, line 2 of the specification. Thus, the Office's assertion that the claimed amino acid sequences differ in structure and function (Office Action of December 22, 2003 at page 2) is incorrect; and thereby does not support Restriction among the different claimed amino acid sequences. The same considerations apply to the claimed nucleic acid sequences (*see* Office Action of December 22, 2003 at page 3), since all possess a common structure (polynucleotide) that is well-correlated with their function of encoding the claimed DNA-binding proteins.

In summary, although the claims possess unity according to MPEP § 803.02, imposition of the present Restriction Requirement(s) has prevented Applicants from claiming the full scope of their invention, and is tantamount to a rejection under 35 U.S.C. § 121, which has long been improper. Accordingly, Restriction among the different claimed sequences, both protein and nucleic acid, should be withdrawn.

Applicants presented a similar argument in their traversal dated January 22, 2004. Although this argument was acknowledged in the Office Action dated March 18, 2004, in which the Restriction Requirement was made final, it was neither further addressed nor rebutted by the Office.

3. *Restriction between proteins and nucleic acids is supported by throwaway utilities*

The Office has admitted on the record that ". . . the DNA molecule and protein are related since the DNA encodes the specifically claimed protein." (Office Action dated December 22, 2003 at page 3.) However, in support of Restriction between claims to proteins and nucleic acids encoding said proteins, the Office alleges that

> ". . .they are distinct inventions because the protein product can be made by another and materially different process, such as by synthetic peptide synthesis or purification from the natural source. Further, the DNA may be used for processes other than the production of the protein, such as nucleic acid hybridization assay." (Office Action dated December 22, 2003 at page 3.)

In their traversal of this particular aspect of the Restriction Requirement, Applicants pointed out that both the claimed proteins and the claimed nucleic acids are non-naturally-occurring molecules. Accordingly, it would be impossible to purify the claimed proteins from a natural source, as asserted by the Office. Applicants additionally provided evidence that current methods of automated peptide synthesis were not capable of reproducibly providing polypeptides having the length of the claimed proteins. (See Applicants Response dated January 22, 2004 at pp. 12-13). Applicants requested that, if the Office maintained the Restriction Requirement, it provide evidence that peptides longer than 90 amino acid residues could be generated by automated methods and identify a natural source of the claimed proteins and nucleic acids. Neither request was addressed in the Office Action of March 18, 2004, in which the Restriction Requirement was made final.

With respect to the Office's assertion that the claimed nucleic acids could be used in a hybridization assay, Applicants pointed out that the claimed nucleic acids encoded

non-naturally-occurring proteins, and that it would therefore be difficult to imagine a specific target of a hybridization assay which used a non-naturally-occurring nucleic acid as a probe. Applicants further requested that the Office specifically identify the target of such a hypothetical hybridization assay. (Response dated January 22, 2004 at pp. 13-14).

The Office has not rebutted these arguments, nor has it identified any specific target for its alleged hybridization assay.

In summary, the attempted restriction between claims to proteins and claims to nucleic acids encoding these proteins has been supported by "throwaway" utilities which are not specific, substantial or credible. To the extent that the Office is asserting that proteins and the nucleic acids encoding them are separate inventions, each alleged invention must have a specific, substantial and credible utility (35 U.S.C. § 101; 66 Fed. Reg. 1092; 1242 OG 162). Since the Office has failed to provide specific, substantial and credible utilities to support its assertion that proteins and nucleic acids are different inventions, restriction therebetween should be withdrawn.

Applicants made similar arguments in their traversal dated January 22, 2004 which were not rebutted by the Office. Moreover, the Office has failed to identify methods of automated peptide synthesis capable of generating the claimed proteins, natural sources of the claimed proteins or a specific target for which the claimed nucleic acids could be used in a hybridization assay, in response to Applicants' request.

4. *Maintenance of the Restriction Requirement would present undue burdens to both Applicants and the Office*

Were Applicants to comply with the Restriction Requirement as it currently stands, it would require the filing of either 29 or 89 additional applications[3]. Were all 30 or 90 of those applications necessitated by this Restriction Requirement to issue as patents, the full scope of Applicants' invention would still not be covered, for the reasons set forth above in Section E.2. At current rates, the filing of 29 applications would cost Applicants $22,330 (in filing fees alone), while the filing of 89 applications would

[3] It is impossible to determine the exact number of additional applications that would need to be filed, due to the lack of clarity of the Restriction requirement

require an expenditure of $68,530 in filing fees, not including excess claim fees. Applicants maintain that such expenditures (in addition to those related to prosecution of 30 or 90 separate applications) constitute an undue burden, especially in light of the fact that the invention would still not be fully covered after having made such expenditures.

Applicants acknowledge the Office's statement (in the Office Action dated March 18, 2004) that sequence searching presents a burden. However, Applicants respectfully inquire whether the necessity to examine 29 or 89 additional applications would not also present a possibly more onerous burden to the Office, especially in light of the current examination backlog.

5. *Conclusion*

For all of the reasons presented above, as well as those presented in their Response dated January 22, 2004, Applicants believe the Restriction Requirement is improper and should be withdrawn. Applicants presented a number of arguments supporting traversal in their response dated January 22, 2004; the majority of which have been neither addressed nor rebutted by the Office. Accordingly, Applicants request that the Restriction Requirement be reviewed by the Director, that it be withdrawn in its entirety, and that Groups 1-90 be rejoined.

Applicants' previous election was improper

Applicants note that the election presented in their response of January 22, 2004 defined a three-finger zinc finger protein in which F1 contains the amino acid sequence DRSNLTR, F2 contains the amino acid sequence TSGHLSR and F3 contains the amino acid sequence RSDHLSR. Having reviewed the Restriction Requirement in connection with the preparation of this Response, Applicants note that a protein containing their elected F1, F2 and F3 sequences was not among the choices presented to Applicants by the Office in the Restriction Requirement. Accordingly, Applicants believe that their election was improper and inadvertently non-responsive.

To correct this inadvertent error, Applicants hereby elect, with traverse, a protein in which F1 has the amino acid sequence RSDNLAR, F2 has the amino acid sequence

RSDNLAR and F3 has the amino acid sequence RSDNLTR, as set forth in the second line of the Table on Page 2 of the Restriction Requirement, and recited in claims 1, 5, 6 and 7. All three of these sequences were disclosed, for example, in priority application 60/126,238 filed on March 24, 1999.

35 U.S.C. § 101

Claims 1, 8, 19 and 23 were provisionally rejected under this section in view of claim 5 of co-owned USSN 10/006,069.

Inasmuch as the election of claims 8, 19 and 23 was improper, the rejection is believed to be moot. Moreover, since USSN 10/006,069 does not claim a three-finger protein in which F1 has the amino acid sequence RSDNLAR, F2 has the amino acid sequence RSDNLAR and F3 has the amino acid sequence RSDNLTR, the rejection does not apply to claims 5, 6 and 7 presently under consideration.

Obviousness-type Double Patenting

Claims 1, 8, 19 and 23 were provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-4, 6-18, and 91-93 of co-owned USSN 10/006,069.

Inasmuch as the election of claims 8, 19 and 23 was improper, the rejection is believed to be moot. Moreover, since USSN 10/006,069 neither discloses nor claims a three-finger protein in which F1 has the amino acid sequence RSDNLAR, F2 has the amino acid sequence RSDNLAR and F3 has the amino acid sequence RSDNLTR, the rejection does not apply to claims 5, 6 and 7 presently under consideration.

35 U.S.C. § 112, second paragraph

Claim 1 was rejected under this section as allegedly indefinite for reciting non-elected subject matter. Applicants respectfully traverse this rejection.

As stated above and in the previous response, the claimed subject matter is directed to a collection of proteins that are defined by particular portions of their amino acid sequence that are responsible for their DNA-binding specificity. The restriction

requirement improperly limits the claimed subject matter to a single protein which binds to only one of over 4,000 different possible target sites. However, the identity of each and every target site is available to one of skill in the art[4] and, for the vast majority of these target sites, a zinc finger protein which binds the target site (or a nucleic acid encoding such a zinc finger protein) is provided, and is clearly described and claimed with respect to its amino acid sequences responsible for binding.

Thus, if claim 1 were to recite only a single protein, out of the many that are disclosed and exemplified, it would actually less clearly claim this aspect of Applicants' invention. Accordingly, Applicants believe the rejection is in error and should be withdrawn.

35 U.S.C. § 102(e)

Claims 1, 8, 19 and 23 were rejected under this section as allegedly anticipated by WO 02/46412 and US Patent Application Publication No. 2003/0021776.

In response, Applicants note that sequences claimed in properly elected claims 5, 6 and 7 were disclosed, at the claimed positions, in priority application 60/126,238 filed on March 24, 1999. Since the priority date of both WO 02/46412 and US 2003/0021776 is December 7, 2000, neither is available as a reference under Section 102(e). Accordingly, this rejection should be withdrawn.

[4] Inasmuch as the target site is defined to contain the sequence GNNGNNGNN and those of skill in the pertinent art know that the designation "N" refers to any one of the four nucleotides A, G, C or T.

CONCLUSION

Applicants regret any inconvenience caused by their inadvertent improper election in response to the Restriction Requirement. A proper, fully responsive election, with traverse, has been provided herein.

Applicants believe the Restriction Requirement, which has been made final, is improper, and petition the Director for review, withdrawal of the Requirement and rejoinder of Groups 1-90.

As set forth herein, Applicants believe that the claims clearly and distinctly recite the subject matter for which a patent is desired, and are free of the cited art.

Respectfully submitted,

Date: July 19, 2004

By: Sean Brennan

Sean M. Brennan
Registration No. 39,917

Sangamo BioSciences, Inc.
501 Canal Blvd., Suite A100
Richmond, California 94804

Telephone: (510) 970-6000 ext. 252
Facsimile: (510) 236-8951